# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FULLER, Grover F., Jr.
Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950
ETATS-UNIS D'AMERIQUE

DEC 12 2005

MOPS PCL Group

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

| Date of mailing *(day/month/year)* | 08.12.2005 |
|---|---|

| Applicant's or agent's file reference | **IMPORTANT NOTIFICATION** |
|---|---|
| PC25264A | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/IB2004/002919 | 06.09.2004 | 17.09.2003 |

Applicant
WARNER-LAMBERT COMPANY LLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

| Name and mailing address of the International preliminary examining authority: | Authorized Officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Ambroa, J.R.<br>Tel. +49 89 2399-8012 |

Form PCT/IPEA/416 (January 2004)

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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference PC25264A | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No. PCT/IB2004/002919 | International filing date *(day/month/year)* 06.09.2004 | Priority date *(day/month/year)* 17.09.2003 |
| International Patent Classification (IPC) or national classification and IPC C07D207/34, A61K31/40, A61P3/06 | | |
| Applicant WARNER-LAMBERT COMPANY LLC et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19.10.2004 | 08.12.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Seymour, L Telephone No. +49 89 2399-8694 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/002919

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

| | |
|---|---|
| **Description, Pages** | |
| 1-16 | as originally filed |
| **Claims, Numbers** | |
| 1-16 | received on 20.07.2005 with letter of 13.07.2005 |
| **Drawings, Sheets** | |
| 1/4-4/4 | as originally filed |

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 15 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-14,16 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item III**

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

**Re Item V**

1. Reference is made to the following documents:

   D1: US-B-6 583 2951 D2: WO-A-02 43667 D3: US-A-4 681 893

2. The subject-matter of the present claims is new (Article 33(2) PCT), since they do not disclose crystalline atorvastatin free acid: in D1 the free acid of atorvastatin is an oil, in D2 it is obtained as a solid mixture with the lactone form, and in D3 it is obtained as a crude material which is not further purified.

3. Document D1 is regarded as being the closest prior art. The present atorvastatin free acid differs from that disclosed in D1 in that it is a crystalline solid rather than an oil (see D1, example 22), which results in a purer, more stable product (see present description, p. 3, lines 27-29 and p. 11, lines 13-17).

   The problem to be solved by the present invention may be regarded as the provision of a purer, more stable form of atorvastatin.

   Previously, this problem has been solved by formation of salts (see D1-D3). The solution to this problem proposed in the present claims is considered as involving an inventive step (Article 33(3) PCT) since none of the prior art suggests the formation of a crystalline form of atorvastatin free acid.

4. Industrial applicability (Article 33(4) PCT)

   For the assessment of the present claim 15 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO,

for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

Claims 2-13 comprise all the features of claims 1 and 16 and are therefore not appropriately formulated as claims dependent on the latter (Article 6 and Rule 6.4 PCT). In addition a reference to claim 1 has been omitted from claim 14.

Contrary to Article 6 PCT, claim 1 does not contain the full chemical name of atorvastatin (cf. p. 1, lines 6-8).

CLAIMS

1. A crystalline atrovastatin free acid.

2. A crystalline Form A atorvastatin free acid or a hydrate thereof having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.9, 20.6, 22.5, or 25.9.

3. A crystalline Form A atorvastatin free acid or a hydrate thereof having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.7, 6.0, 8.9, 9.1, 9.4, 13.2, 14.1, 17.8, 18.1, 18.9, 19.9, 20.2, 20.6, 21.8, 22.1, 22.5, 23.7, 25.9, and 26.7.

4. A crystalline Form A atorvastatin free acid ~~hydrate thereof~~ having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.9, 20.6, 22.5, or 25.9.

5. A crystalline Form A atorvastatin free acid ~~hydrate thereof~~ having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.7, 6.0, 8.9, 9.1, 9.4, 13.2, 14.1, 17.8, 18.1, 18.9, 19.9, 20.2, 20.6, 21.8, 22.1, 22.5, 23.7, 25.9, and 26.7.

6. A crystalline Form A atorvastatin free acid or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 18.1, 18.8, 20.5, and 21.2.

7. A crystalline Form A atorvastatin free acid or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 161.5, 163.6, 166.3, 167.1, 174.3, and 180.6.

8. A crystalline Form A atorvastatin free acid or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 18.1, 18.8, 20.5, 21.2, 25.0, 25.5, 26.2, 26.8, 37.1, 38.9, 40.0, 40.6, 41.8, 42.9, 43.5, 65.3, 68.6, 69.1, 70.0, 71.3, 112.3, 113.7, 115.1, 116.4, 118.4, 119.3, 121.6, 123.3, 125.4, 128.0, 128.8 (shoulder), 130.0, 132.9, 134.1, 135.2, 137.9, 140.7, 141.8, 161.5, 163.6, 166.3, 167.1, 174.3, and 180.6.

9. A crystalline Form A atorvastatin free acid or a hydrate thereof characterized by solid-state $^{19}F$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: -114.1, -112.6, -110.6, ~~or~~ and -105.6.

10. A crystalline Form A atorvastatin free acid ~~hydrate thereof~~ characterized by solid-state $^{19}F$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: -114.1, -112.6, -110.6, ~~or~~ and -105.6.

11. A crystalline Form B atorvastatin free acid or a hydrate thereof having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.6, 17.4, 21.1, ~~or~~ and 21.5.

12. A crystalline Form B atorvastatin free acid or a hydrate thereof having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.6, 5.9, 8.6, 9.3, 13.3, 14.1, 17.4, 17.7, 18.0, 18.8, 19.3, 19.8, 20.2, 21.1, 21.5, 21.9, and 23.6.

13. A crystalline Form B atorvastatin free acid having a X-ray powder diffraction pattern containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.6, 5.9, 8.6, 9.3, 13.3, 14.1, 17.4, 17.7, 18.0, 18.8, 19.3, 19.8, 20.2, 21.1, 21.5, 21.9, and 23.6.

14. A pharmaceutical composition comprising crystalline atrovastatin free acid in admixture with at least one pharmaceutically acceptable excipient, diluent, or carrier.

15. A method of treating hyperlipidemia, hypercholesterolemia, osteoporosis, benign prostatic hyperplasia, and Alzheimer's Disease comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

16. A crystalline atorvastatin free acid hydrate.